Update in Adult Asthma

Current Guidelines and Introduction to Advanced Therapies

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Goals and Objectives

- Review steps in asthma diagnosis
- Be able to classify asthma severity and control
- Understand how to use the NAEPP guidelines to adjust medications
- Discuss options for and evidence supporting advanced asthma therapies

National Asthma Education and Prevention Program

National Heart, Lung, and Blood Institute

Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma

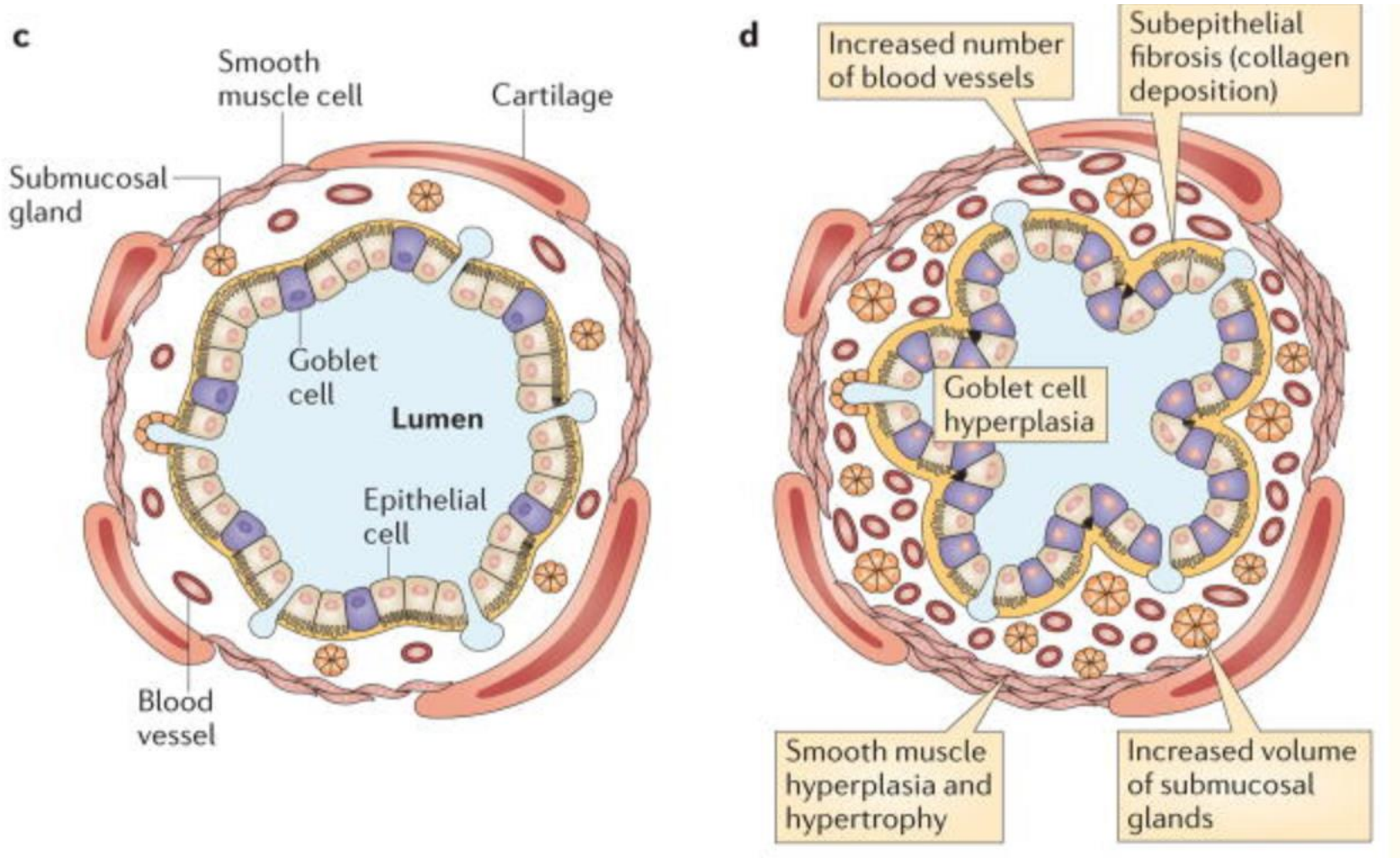
Full Report 2007

TASK FORCE REPORT
ERS/ATS GUIDELINES ON SEVERE ASTHMA

International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma

What is Asthma?

- Chronic disorder of the airways characterized by:
  - Recurring symptoms
  - Airflow obstruction
  - Bronchial hyperresponsiveness
  - Underlying inflammation



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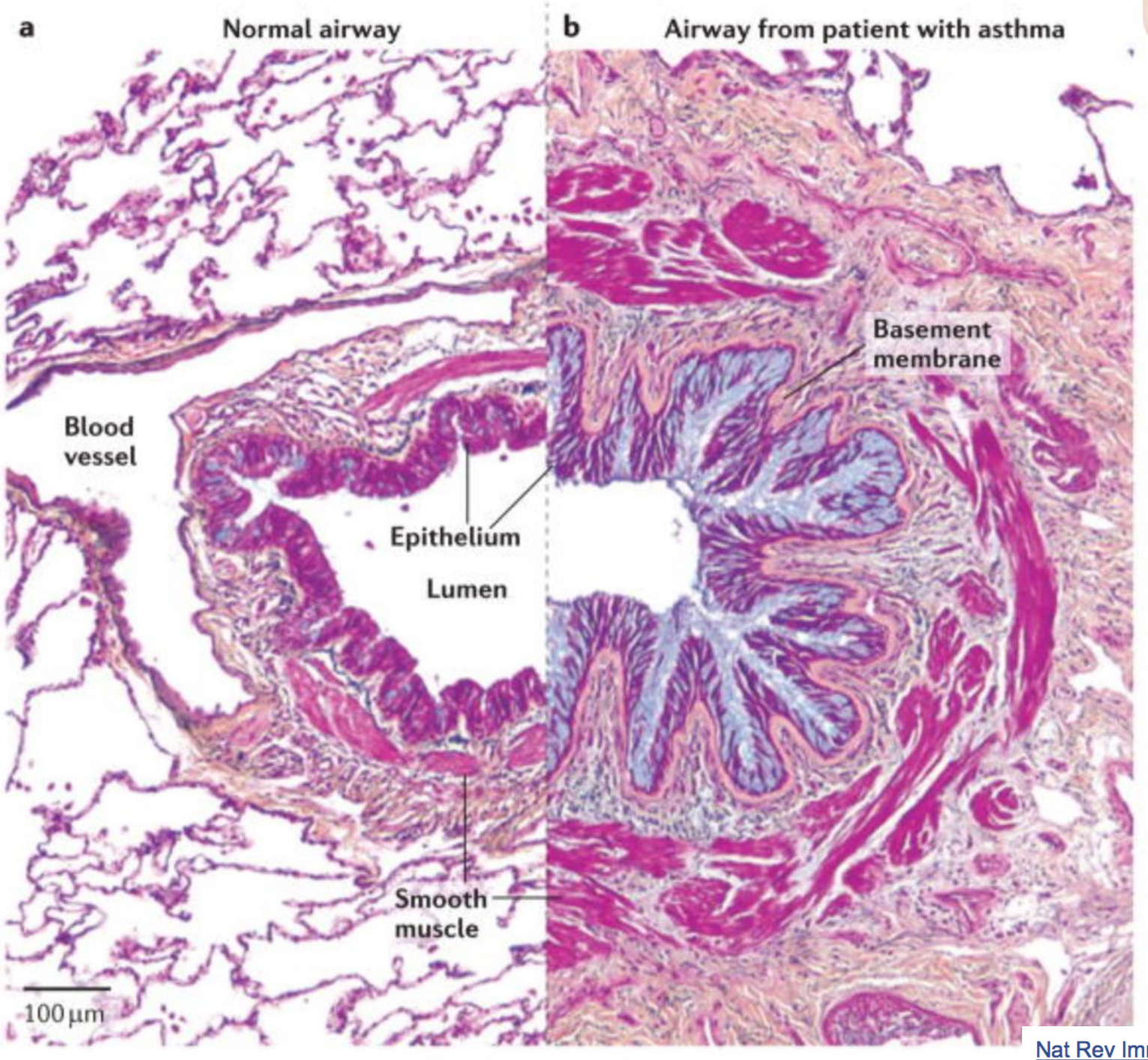
Nat Rev Immunol. 2015 Jan; 15(1): 57–65.



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Mechanisms of obstruction

1. Contraction of smooth muscle
2. Airway wall thickening due to edema
3. Plugging of airway with mucus or cellular debris
4. Airway remodeling

Asthma Diagnosis

Diagnosis of asthma: Symptoms

- *Increased* probability that symptoms are due to asthma if:
  - More than one type of symptom (wheeze, shortness of breath, cough, chest tightness)
  - Symptoms often worse at night or in the early morning
  - Symptoms vary over time and in intensity
  - Symptoms are triggered by viral infections, exercise, allergen exposure, changes in weather, laughter, irritants such as car exhaust fumes, smoke, or strong smells
- *Decreased* probability that symptoms are due to asthma if:
  - Isolated cough with no other respiratory symptoms
  - Chronic production of sputum
  - Shortness of breath associated with dizziness, light-headedness or peripheral tingling
  - Chest pain
  - Exercise-induced dyspnea with noisy inspiration (stridor)

Diagnosis of asthma: Pulmonary Function Test

- NAEPP recommends that spirometry be performed with bronchodilator for patients in whom diagnosis of asthma is being considered

Spirometry

	PRED	L.L.N.	PRE	PRE % PRED	POST	POST % PRED	%CHANGE
FVC	4.02	> 3.25	3.19 <	79 <	3.65	91	14
FEV.5	2.38	> 1.87	1.45 <	61 <	1.78 <	75 <	22
FEV1	3.19	> 2.54	1.99 <	62 <	2.46 <	77 <	24
FEV1/FVC	81	> 71	62 <	77 <	67 <	84	8

Confirmation of asthma in an era of overdiagnosis

Eur Respir J 2010; 36: 255–260
DOI: 10.1183/09031936.00165109

V.P. Luks*, K.L. Vandemheen# and S.D. Aaron#

JAMA | Original Investigation

Reevaluation of Diagnosis in Adults With Physician-Diagnosed Asthma

JAMA. 2017;317(3):269-279. doi:10.1001/jama.2016.19627

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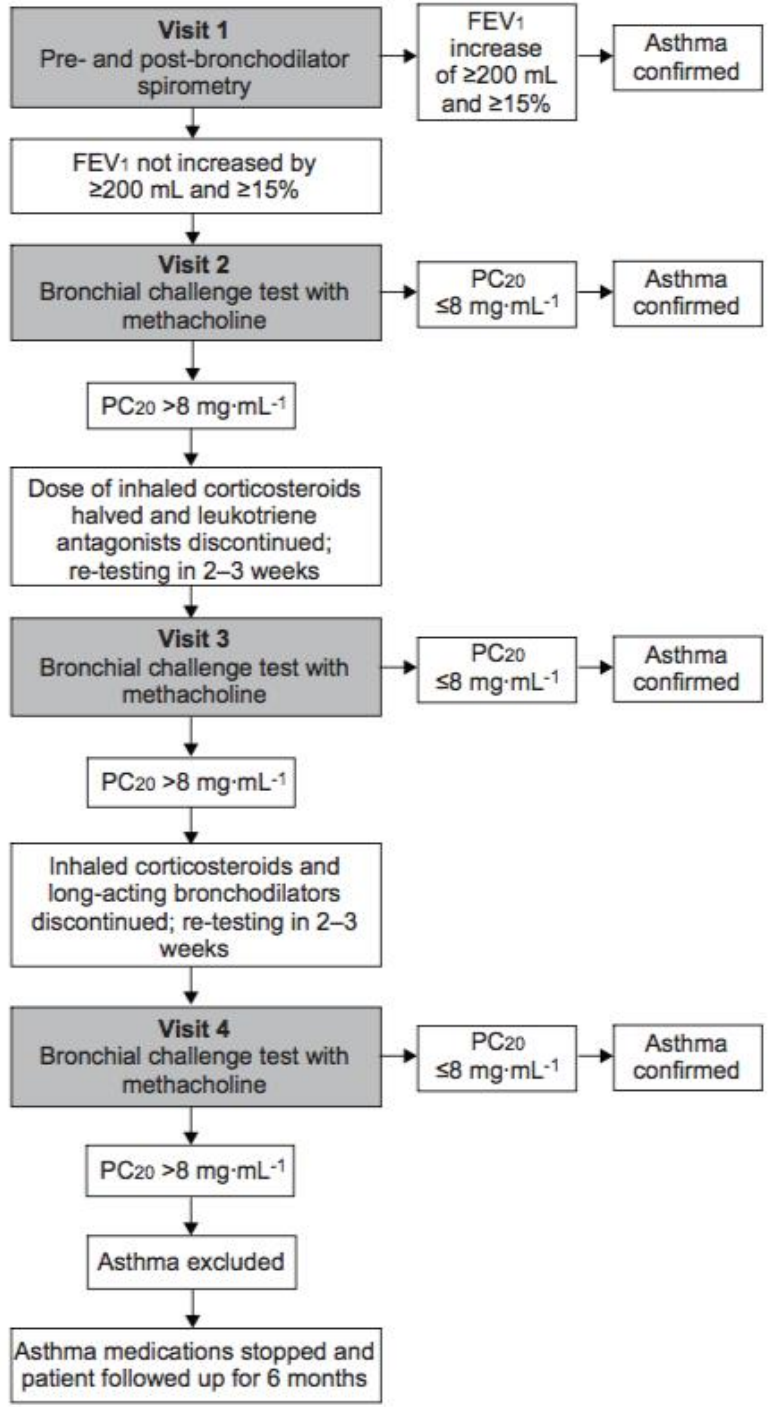
Bronchial Provocation Challenge

- NAEPP recommends performing if considering other diagnoses
- Increasing concentrations of provocative agent inhaled via nebulizer
- Dose that results in a 20% drop in FEV1 is noted (PC20)

- Sensitivity for PC20< 16 mg/mL approaches 100%
- Positive predictive value at 8mg/ml 50%
- False positives: allergic rhinitis, CF, heart failure, COPD, bronchitis



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- 540 patients with asthma diagnosed recruited from community
- 69% asthma confirmed
- 30% asthma not confirmed (66% remained off asthma meds for 6 months)

JAMA | Original Investigation

Reevaluation of Diagnosis in Adults With Physician-Diagnosed Asthma

JAMA. 2017;317(3):269-279. doi:10.1001/jama.2016.19627

- 701 patients with asthma diagnosed recruited from community
- 33% asthma not confirmed (6 patients required asthma meds one year)

Asthma Differential Diagnosis

Dysfunctional breathlessness/vocal cord dysfunction
Chronic obstructive pulmonary disease
Hyperventilation with panic attacks
Bronchiolitis obliterans
Congestive heart failure
Adverse drug reaction (*e.g.* angiotensin-converting enzyme inhibitors)
Bronchiectasis/cystic fibrosis
Hypersensitivity pneumonitis
Hypereosinophilic syndromes
Pulmonary embolus
Herpetic tracheobronchitis
Endobronchial lesion/foreign body (*e.g.* amyloid, carcinoid, tracheal stricture)
Allergic bronchopulmonary aspergillosis
Acquired tracheobronchomalacia
Churg–Strauss syndrome

https://sciencing.com/walking-stick-bug-5093235.html
Eur Respir J 2014; 43: 343–373

Asthma Management

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Four Components of Asthma Management

NAEPP Guidelines

1. Assess and monitor asthma severity and control
2. Asthma self-management education
3. Control of environmental factors and comorbid conditions
4. Medications

Asthma Management

Classify Asthma Severity

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Classify Asthma Severity

- Assess Impairment
  - Symptoms of nighttime awakenings, rescue inhaler usage, missing work
  - Pulmonary function tests

- Assess Risk of Exacerbations
  - Severe or persistent airflow obstruction
  - 2+ ED visits in past year or ANY history of ICU admit or intubation
  - Patient reporting feeling frightened by their asthma
  - Current smoking
  - Attitudes and beliefs about taking medications

Components of Severity		Classification of Asthma Severity ≥12 years of age			
			Persistent		
		Intermittent	Mild	Moderate	Severe
Impairment **Normal FEV_1/FVC:** **8–19 yr 85%** **20–39 yr 80%** **40–59 yr 75%** **60–80 yr 70%**	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x/month	3–4x/month	>1x/week but not nightly	Often 7x/week
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily, and not more than 1x on any day	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	• Normal FEV_1 between exacerbations • FEV_1 >80% predicted • FEV_1/FVC normal	• FEV_1 >80% predicted • FEV_1/FVC normal	• FEV_1 >60% but <80% predicted • FEV_1/FVC reduced 5%	• FEV_1 <60% predicted • FEV_1/FVC reduced >5%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year (see note)	≥2/year (see note) →		
		← Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. Relative annual risk of exacerbations may be related to FEV_1.			
Recommended Step for Initiating Treatment **(See figure 4–5 for treatment steps.)**		**Step 1**	**Step 2**	**Step 3** and consider short course of oral systemic corticosteroids	**Step 4 or 5** and consider short course of oral systemic corticosteroids
		In 2–6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.			

Patient Case

- 22 year old female
- Cough and chest tightness during inversion and “with colds”
- Using albuterol daily for shortness of breath for past 2 weeks
- Never hospitalized for asthma
- Exam with scattered end expiratory wheezing
- PFTs with mild obstruction and significant bronchodilator response

Classification of Asthma Severity ≥12 years of age

Components of Severity		Intermittent	Persistent: Mild	Persistent: Moderate	Persistent: Severe
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Asthma Management

Assessing Control

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Asthma Control

Goals of therapy

- Minimal or no chronic symptoms day or night
- Minimal or no exacerbations
- No limitations on activities
- Maintenance of (near) normal pulmonary function
- Minimal use of short-acting inhaled beta2-agonist

Clarification: Severity vs Control

"Interpretation of previous guidelines raised questions about applying the severity classifications once treatment is established and also resulted in placing more emphasis on severity than on ongoing monitoring of whether therapeutic goals were being met"

- When initiating treatment, classify severity and use to choose initial therapy
- Once treatment is established, emphasis is on assessing asthma control and adjusting therapy appropriately

SCORE

1. In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school or at home?

All of the time **[1]**	Most of the time **[2]**	Some of the time **[3]**	A little of the time **[4]**	None of the time **[5]**	.....

2. During the past 4 weeks, how often have you had shortness of breath?

More than Once a day **[1]**	Once a day **[2]**	3 to 6 times a week **[3]**	Once or twice a week **[4]**	Not at all **[5]**	.....

3. During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?

4 or more nights a week **[1]**	2 to 3 nights a week **[2]**	Once a week **[3]**	Once or twice **[4]**	Not at all **[5]**	.....

4. During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?

3 or more times per day **[1]**	1 to 2 times per day **[2]**	2 or 3 times per week **[3]**	Once a week or less **[4]**	Not at all **[5]**	.....

5. How would you rate your asthma control during the past 4 weeks?

Not Controlled at All **[1]**	Poorly Controlled **[2]**	Somewhat Controlled **[3]**	Well Controlled **[4]**	Completely Controlled **[5]**	.....

TOTAL: .....

Patient Case

- You start therapy and follow-up in clinic in 6 weeks…

- No nighttime awakenings
- Using albuterol about once per week
- ACT score 23
- Spirometry normal

Components of Control		Classification of Asthma Control (Youths ≥12 years of age and adults)		
		Well-Controlled	**Not Well-Controlled**	**Very Poorly Controlled**
Impairment	Symptoms	≤2 days/week	>2 days/week	Throughout the day
	Nighttime awakening	≤2x/month	1–3x/week	≥4x/week
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week	Several times per day
	FEV_1 or peak flow	>80% predicted/ personal best	60–80% predicted/ personal best	<60% predicted/ personal best
	Validated Questionnaires ATAQ ACQ ACT	 0 ≤0.75* ≥20	 1–2 ≥1.5 16–19	 3–4 N/A ≤15
Risk	Exacerbations	0–1/year	≥2/year (see note)	
		Consider severity and interval since last exacerbation		
	Progressive loss of lung function	Evaluation requires long-term followup care		
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		

Asthma Management

Self-management

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Asthma Action Plan

Green Zone: Doing Well

Symptoms: Breathing is good – No cough or wheeze – Can work and play – Sleeps well at night

Peak Flow Meter _____ (more than 80% of personal best)

Control Medicine(s)	Medicine	How much to take	When and how often to take it
	_____	_____	_____
	_____	_____	_____

Physical Activity

☐ Use albuterol/levalbuterol ____ puffs, 15 minutes before activity

☐ with all activity ☐ when you feel you need it

Yellow Zone: Caution

Symptoms: Some problems breathing – Cough, wheeze, or chest tight – Problems working or playing – Wake at night

Peak Flow Meter _____ to _____ (between 50% and 79% of personal best)

Quick-relief Medicine**(s)** ☐ Albuterol/levalbuterol ____ puffs, every 4 hours as needed

Control Medicine**(s)**

☐ Continue Green Zone medicines

☐ Add _____ ☐ Change to _____

You should feel better within 20–60 minutes of the quick-relief treatment. If you are getting worse or are in the Yellow Zone for more than 24 hours, THEN follow the instructions in the RED ZONE and call the doctor right away!

Asthma Action Plan

Red Zone: Get Help Now!

Symptoms: Lots of problems breathing – Cannot work or play – Getting worse instead of better – Medicine is not helping

Peak Flow Meter _____ (less than 50% of personal best)

Take Quick-relief Medicine NOW! ☐ Albuterol/levalbuterol ____ puffs, _____ (how frequently)

Call 911 immediately if the following danger signs are present

- Trouble walking/talking due to shortness of breath
- Lips or fingernails are blue
- Still in the red zone after 15 minutes

https://www.nhlbi.nih.gov/files/docs/public/lung/asthma_actplan.pdf

http://www.lung.org/assets/documents/asthma/asthma-action-plan.pdf

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Peak Flow Meters

- Asthma action plans can be based on symptoms or peak flow meter
  - Two methods are equally effective
- May be helpful in patients with poor perception of asthma symptoms

Inhaler Technique

- 2016 review of inhaler technique:
  - 31% of patient with correct inhaler technique
  - 41% acceptable inhaler technique
  - 31% poor inhaler technique
- Spacer can help in coordinating actuation and inhalation

- Reviewing inhaler technique is very important, but takes time and new inhalers delivery systems are on the market
  - https://www.cdc.gov/asthma/inhaler_video/default.htm
  - Drug company website videos can be helpful
  - Seek help from pharmacist, nursing staff etc

Environmental Factors and Comorbid Conditions

Controlling Exacerbating Factors

- Reduce exposure to allergens to which patient is sensitized
- Avoid exposure to respiratory irritants (tobacco smoke, fire etc)
- Avoid exertion outside when pollution is high
- Consider allergen immunotherapy

- Evaluate comorbidities: GERD, OSA, ABPA, rhinitis/ sinusitis, chronic stress/depression, obesity

Asthma Management

Medications

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Case

- 22 year old female
- Cough and chest tightness during inversion and with colds
- Using albuterol prn frequently
- ACT score 12
- Exam with scattered end expiratory wheezing
- PFTs with mild obstruction and significant BD response

- Moderate persistent

Classification of Asthma Severity ≥12 years of age

Components of Severity		Intermittent	Persistent: Mild	Persistent: Moderate	Persistent: Severe
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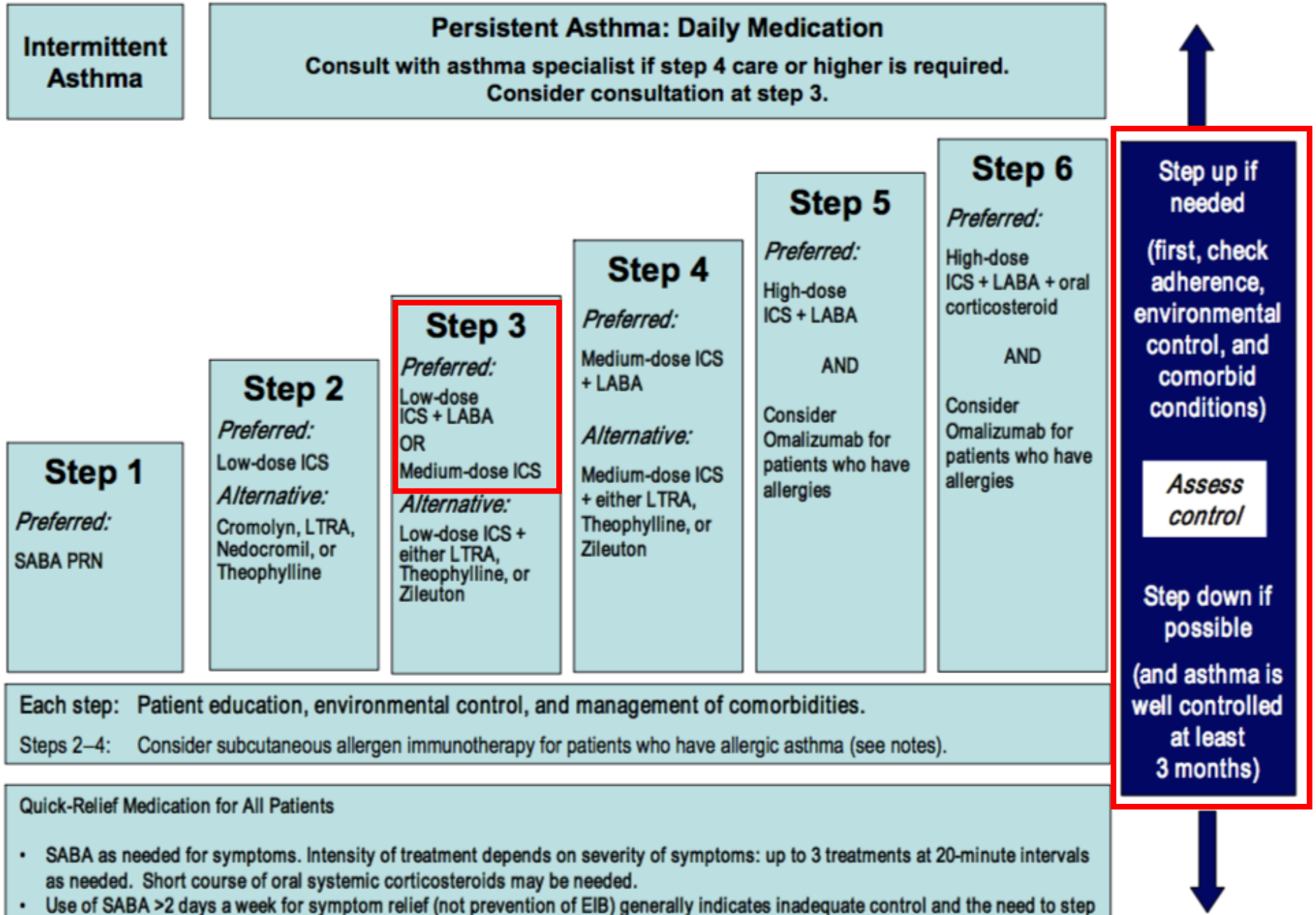
Intermittent Asthma
Persistent Asthma: Daily Medication
Consult with asthma specialist if step 4 care or higher is required.
Consider consultation at step 3.
Step 1
Preferred:
SABA PRN
Step 2
Preferred:
Low-dose ICS
Alternative:
Cromolyn, LTRA, Nedocromil, or Theophylline
Step 3
Preferred:
Low-dose ICS + LABA
OR
Medium-dose ICS
Alternative:
Low-dose ICS + either LTRA, Theophylline, or Zileuton
Step 4
Preferred:
Medium-dose ICS + LABA
Alternative:
Medium-dose ICS + either LTRA, Theophylline, or Zileuton
Step 5
Preferred:
High-dose ICS + LABA
AND
Consider Omalizumab for patients who have allergies
Step 6
Preferred:
High-dose ICS + LABA + oral corticosteroid
AND
Consider Omalizumab for patients who have allergies
Step up if needed
(first, check adherence, environmental control, and comorbid conditions)
Assess control
Step down if possible
(and asthma is well controlled at least 3 months)
Each step: Patient education, environmental control, and management of comorbidities.
Steps 2–4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma (see notes).
Quick-Relief Medication for All Patients
• SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed.
• Use of SABA >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.

Consider Antileukotriene Agent

- Leukotriene receptor antagonist: Leukotrienes induce smooth muscle contraction, promote mucus gland secretion, promote leukocyte infiltration
- Montelukast (Singulair) and zafirlukast (Accolate): leukotriene receptor antagonists
- Zilueton (Zyflo): inhibits formation of leukotriene
- Clinical use:
  - Superior to placebo as monotherapy in mild asthma
  - Inferior to ICS as monotherapy

Antileukotriene Agents
specific groups

- Aspirin exacerbated respiratory disease
- Exercise-induced asthma
- Viral URI-induced symptoms
- Symptoms triggered by air pollution
- Allergic rhinitis
- Obesity: theoretical, not proven in studies

Who should be referred to asthma specialist?

- Life threatening asthma exacerbation
- Patient not meeting goals after 3-6 months of treatment
- Atypical signs or symptoms
- Complicating diagnoses (VCD, ABPA, severe rhinitis)
- Patient requires step 4 or higher to maintain control
- Two or more corticosteroid bursts in one year

VCD: Vocal cord dysfunction
ABPA: Allergic bronchopulmonary aspergillosis

Severe Asthma

Diagnosis and Management

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ATS Definition of Severe Asthma

Asthma which requires treatment with guidelines suggested medications for steps 4–5 asthma for the previous year or systemic CS for >50% of the previous year to prevent it from becoming ‘‘uncontrolled’’ or which remains ‘‘uncontrolled‘‘ despite this therapy

Uncontrolled asthma defined as at least one of the following:

1) Poor symptom control: ACT < 20

2) Frequent severe exacerbations: two or more bursts of systemic CS in the previous year

3) Serious exacerbations: at least one hospitalization, ICU stay or mechanical ventilation in the previous year

4) Airflow limitation: after appropriate bronchodilator withhold FEV1 <80% predicted (in the face of reduced FEV1/FVC defined as less than the lower limit of normal)

Controlled asthma that worsens on tapering of these high doses of ICS or systemic CS (or additional biologics)

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Eur Respir J 2014; 43: 343–373

Severe Asthma Management
Step 1: Determine that the patient has asthma

Dysfunctional breathlessness/vocal cord dysfunction
Chronic obstructive pulmonary disease
Hyperventilation with panic attacks
Bronchiolitis obliterans
Congestive heart failure
Adverse drug reaction (*e.g.* angiotensin-converting enzyme inhibitors)
Bronchiectasis/cystic fibrosis
Hypersensitivity pneumonitis
Hypereosinophilic syndromes
Pulmonary embolus
Herpetic tracheobronchitis
Endobronchial lesion/foreign body (*e.g.* amyloid, carcinoid, tracheal stricture)
Allergic bronchopulmonary aspergillosis
Acquired tracheobronchomalacia
Churg–Strauss syndrome

https://sciencing.com/walking-stick-bug-5093235.html
Eur Respir J 2014; 43: 343–373

Severe Asthma Management

Step 2: Assess comorbidities and contributing factors

- Inhaler compliance (inhaler cost)
- Inhaler teaching
- Comorbidities:
  - Obesity
  - Rhinosinusitis/ nasal polyps
  - Vocal cord dysfunction
  - OSA
  - GERD (symptomatic)
  - Smoking

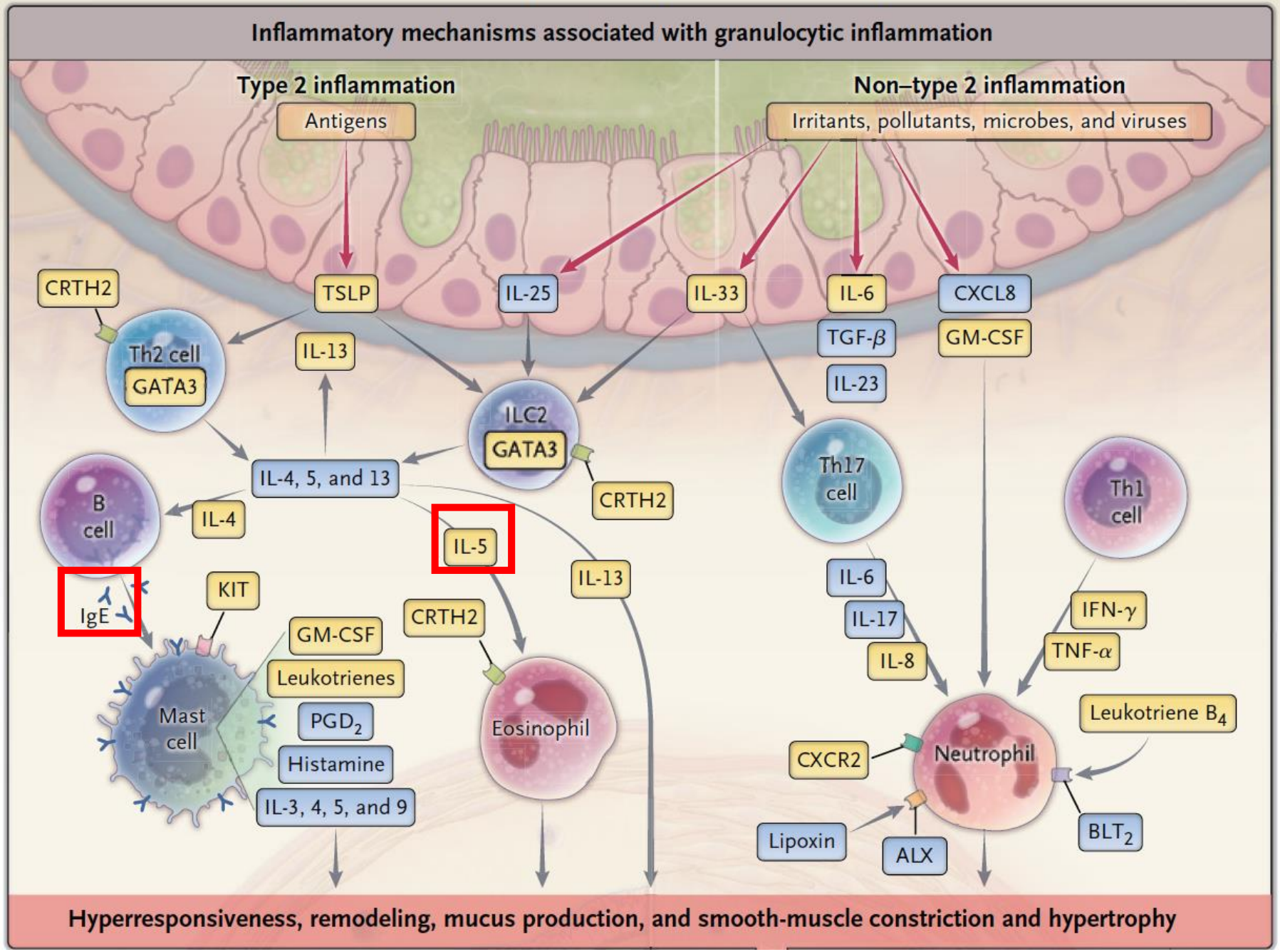
Persistent Uncontrolled Asthmatics

What are the options?

- Biologics
  - Anti-IgE therapy
    - omalizumab (Xolair)
  - Interleuken-5 targets
    - mepolizumab (Nucala)
    - reslizumab (Cinqair)
    - benralizumab (Fasenra)
- Bronchial thermoplasty

Asthma Biologics

Inflammatory mechanisms and pathobiologic features leading to severe asthma



Omalizumab (Xolair)

- Monoclonal antibody that binds IgE
- Approved for:
  - 6+ years old
  - Moderate-severe persistent asthma inadequately controlled with ICS
  - IgE 30-700
  - Allergy testing positive for perennial allergen (dust mites etc.)
- Reduces exacerbation rate
- Reduces glucocorticoid dose

Xolair pearls

- Serum IgE levels increase during Xolair treatment and do not predict response to treatment
- Dose and frequency based on weight and IgE level
- Duration of therapy not well defined
- Cost is $10,000- 70,000 per year

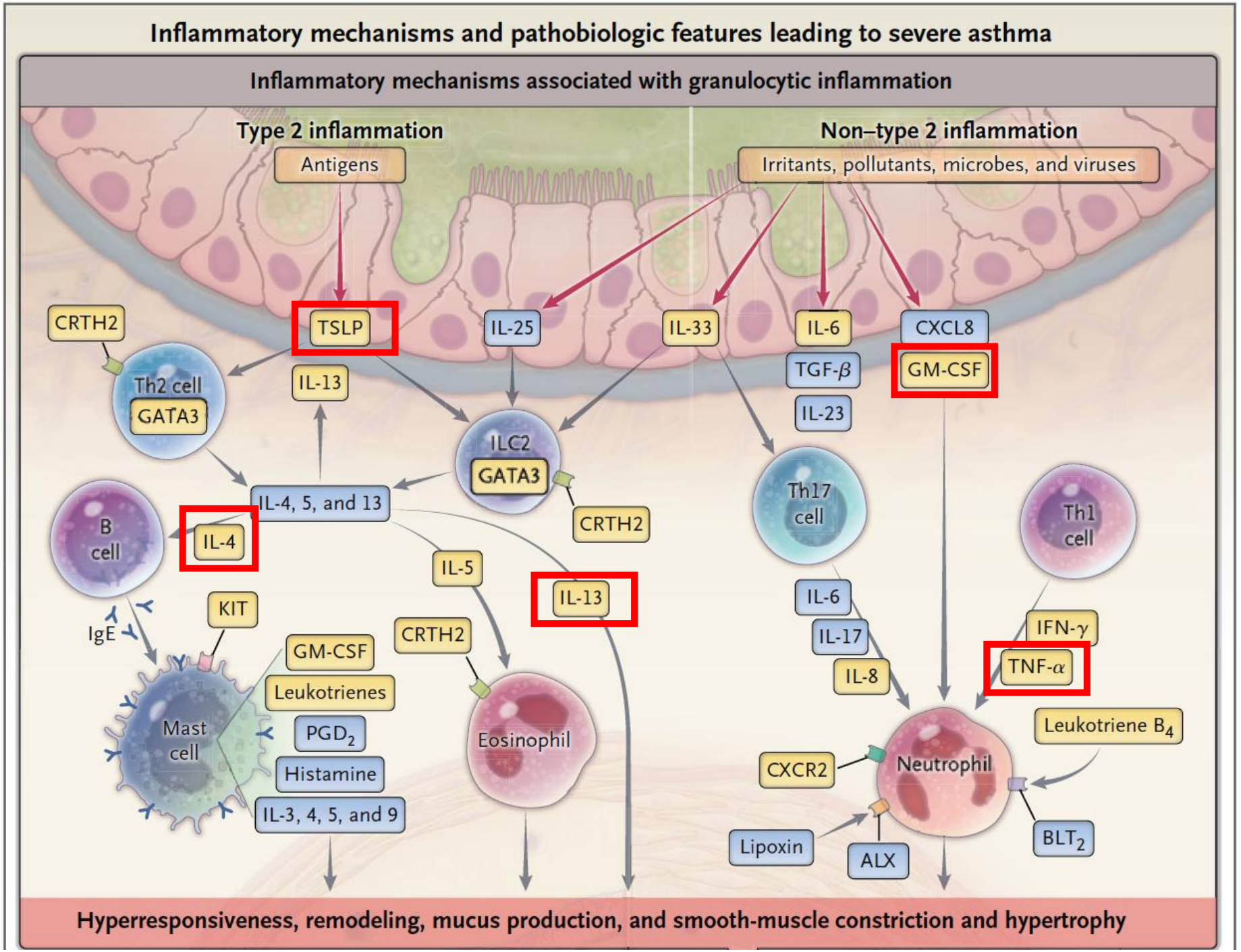
Interleukin 5 biologics: Eosinophilic asthma

- Eosinophil count as low as 150/ul used in studies
- Groups with eosinophil counts >500/ul had more robust response
- Greater benefit in those with frequent exacerbations
- Outcomes:
  - Decreased exacerbation rate
  - Improved quality of life
  - Variable effect on pulmonary function tests

Eosinophilic Asthma

Interleukin 5 biologics

- Mepolizumab (Nucala): anti-IL 5 monoclonal Ab
  - 100mg q4 weeks SC
- Reslizumab (Cinqair): anti-IL 5 monoclonal Ab
  - IV infusion q 4 weeks
- Benralizumab (Fasenra): anti IL-5 receptor Ab
  - 30mg SC q 4 weeks x 3 doses, then q 8 weeks



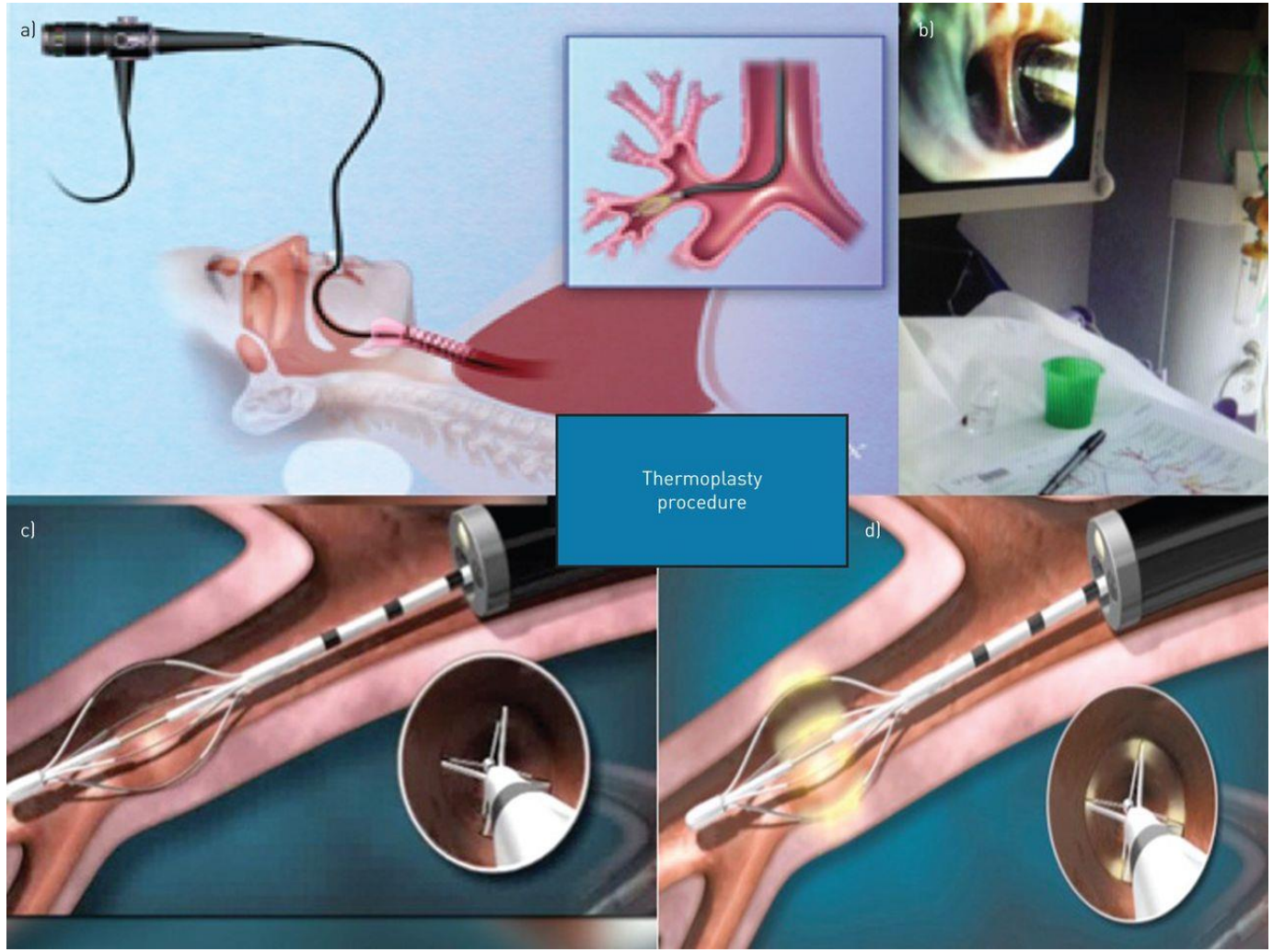
Bronchial Thermoplasty

- Approved in 2010
- Applies heat via radiofrequency waves to the airway
- Three separate procedures under moderate or general anesthesia

- Biopsy studies have shown decreased smooth muscle in airways post-procedure
- May effect secretion of inflammatory mediators, but not studied in humans

- http://www.btforasthma.com/physicians/how-it-works.html

Bronchial thermoplasty procedure. a) Bronchial thermoplasty is performed through fibreoptic bronchoscopy. b) A catheter is inserted in a proximal bronchus. c) The catheter is opened in situ. d) The catheter delivers controlled thermal energy.



Marie-Christine Dombret et al. Eur Respir Rev 2014;23:510-518

Bronchial Thermoplasty Trials

- AIR Trial 2008
  - 112 patients moderate-severe asthma, randomized to BT or control
  - BT reduced exacerbations, improved quality of life scores
  - No change in FEV1, bronchial hyperresponsiveness, symptom free days

- AIR-2 2009
  - 297 patients sham-controlled, randomized, double blind
  - At one year: fewer severe exacerbations, improved QOL
  - Followed at 2 and 5 years for safety
    - No increase in hospital visits or ER visits
    - No change in FVC or FEV1
    - Decreased exacerbations, ER visit, inhaler requirement when compared to year prior

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